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RESEARCH ARTICLE/ARAŞTIRMA YAZISI

USEFULNESS AND PREDICTIVE POWER OF MEMORIAL SLOAN-KETTERING CANCER CENTER NOMOGRAM IN NON-SENTINEL LYMPH NODE METASTASES OUT OF SENTINEL LYMPH NODE METASTASED BREAST CANCER PATIENTS

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ABSTRACT

Purpose: In breast carcinoma, axillary metastasis is the leading prognostic factor. While axillary dissection (AD) is performed in patients with sentinel lymph node (SLN) involvement, there are patients without non-sentinel lymph node (non-SLN) involvement.

To define the predicting power and availability of the nomogram, this has been developed in Memorial Sloan-Kettering Cancer Center by Zee et al, in non-SLN involved patients among breast cancer patients with SLN involvement.

Patients and Methods: The variables used in Memorial Sloan-Kettering Cancer Center nomogram (pathologic size, type, nuclear grade, lymphovascular invasion, multifocality, estrogen receptor positivity of the tumor, defining methods of SLN metastases, positive and negative SLN numbers) are evaluated. The predicted values are compared with the real non-SLN metastases.

Results: While there was no SLN metastases in seventeen patients (45.94%) out of 37, the remaining 20 patients (54.05%) were observed to have non-SLN involvement. When the nomogram is applied, statistically significant involvement was observed in over 70% of patients with non-SLN involvement probability (p=0.022).

Discussion: This nomogram can help to predict the non-SLN metastases in breast carcinoma patients. However, it is not adequate to inform patients about non-performance of AD preoperatively. New studies are required to abstain from AD due to non-SLN involvement by preoperative data.

Key words: Breast carcinoma, axillary lymph node, sentinel lymph node

SENTİNEL LENF NODU TUTULUMU OLAN MEME KARSİNOMLU HASTALARDA DİĞER LENF NODLARININ TUTULUMUNU TAHMİN ETMEK İÇİN MEMORIAL SLOAN-KETTERING CANCER MERKEZİNDE GELİŞTİRİLEN NOMOGRAMIN KULLANILABİLİRLİĞİ

ÖZET

Amaç: Meme karsinomunda, aksiller lenf nodu tutulumu olması prognozu etkileyen önemli faktörlerden biridir. Sentinel lenf nodu (SLN) tutulumu olan hastalarda aksiler disseksiyon (AD) yapılmakla birlikte, aralarında non-sentinel lenf nodu (non-SLN) tutulumu olmayan hastalar bulunmaktadır.

Memorial Sloan-Kettering Cancer Merkezinde, Zee ve arkadaşları tarafından SLN tutulumu olan meme kanserli hastalarda non-SLN tutulumu olan hastaları tahmin etmek için geliştirilen nomogram hastalarımıza uygulayarak, bu nomogramın kullanılabilirliğini tespit etmek.

Hastalar ve Yöntem: Nomogramda kullanılan veriler (hastaların patoloji piyesinde belirtilen tümörün boyutu, tümör tipi ve nükleer grad, lenfovasküler invazyon, multifokalite, östrojen reseptör pozitifliği, SLN metastazını tespit etme yöntemi, pozitif ve negatif SLN sayısı) incelendi. Bu bulgular ile nomogramda belirtilen puanlama sistemi kullanılarak hastalarda non-SLN tutulumu tahmin değerleri tespit edildi. Hastalardaki gerçek non-SLN tutulumu ile bulunan tahmini değerler karşılaştırıldı.

Bulgular: SLN tutulumu olan 37 hastanın 17 (45.94%)' sinde non-SLN tutulumu olmazken, geriye kalan 20 (54.05%) hastada non-SLN tutulumu olduğu görüldü. Nomogram uygulandığında, non-SLN tutulumu olma ihtimalinin 70%' den fazla olduğu tespit edilen hastalarda istatistiksel anlamlı olarak tutulumu olduğu görüldü (p=0.022).

Tartışma: Bu nomogram, SLN tutulumu olan meme karsinomlu hastalarda non-SLN tutulumunu tahmin etmekte yardımcı olabilir. Fakat, ameliyat öncesi hastalara AD yapmama hakkında bilgi vermek için yeterli değildir. Ameliyat öncesi veriler ile non-SLN tutulumunu öngörerek AD' dan kaçınmak için yeni çalışmalar da gerekmektedir.

Anahtar sözcükler: Meme kanseri, aksiller lenf nodu, sentinel lenf nodu

Introduction

Although there are some morbidities of axillary dissection (AD), axillary lymph node (ALN) involvement in breast cancer is an important prognostic factor, which carries significance in staging the disease and making the treatment decision. As sentinel lymph node (SLN) biopsy techniques are developed, AD is not completed in patients with negative axillary nodes. Despite non-involvement of SLN, other non-sentinel lymph node (non-SLN) involvement among patients with SLN involvement differs between 20-70% (1, 2, 3). Van Zee et al. have developed a nomogram at the Memorial Sloan-Kettering Cancer Center (MSKCC), which will help to define risk factors affecting non-SLN involvement in patients with SLN involvement. Definition of this nomogram is based on eight histopathological factors of the primary tumors, namely: pathological measurement, histological type, nuclear grade, presence of lymphovascular invasion, multifocality, estrogen receptor positivity, number of involved or uninvolved lymph nodes, and SLN (4). While Lamber et al. confirmed that nomogram developed in MSKCC was competent, Kocsis et al. denoted that this nomogram was incompetent in the patients that they have employed (5, 6). This present study is conducted to define patients with non-SLN involvement among patients with SLN involvement by the nomogram developed by Zee et al., and to assess if AD may have been avoided in these patients. Availability and validity of this nomogram in our patients has been investigated.

Patients and Methods

Patients with SLN involvement, on whom AD was performed between dates 1 January 2004 – 31 November 2008, were investigated retrospectively. Methylene blue was injected in order to define periareolar SLN. After 5 minutes, SLN was reached by fixing stained lymphatic canal through an axillary or a mastectomy incision. Patients with SLN metastases have undergone AD and we have tested MSKCC nomogram to predict the probability of non-SLN metastases in our SLN biopsy positive patients. Tumor size, tumor type and nuclear grade, lymphovascular invasion, multifocality, estrogen receptor positivity, definition method of SLN metastasis, positive and negative SLN numbers of pathology samples from patients were investigated by the nomogram. By using both the findings of patients and scoring system in the nomogram, non-SLN predictions of patients have been defined in percentages. Real non-SLN involvement rates have been compared with the defined predictive values.

Results

While there was no SLN involvement in 17 out of 37 patients (45.94%), non-SLN involvement was observed in the rest 20 patients (54.05%). When data used in the nomogram were evaluated, only increase in SLN-involvement number is observed to cause a statistically increase in non-SLN number (p=0.048, Mann

		Non-SLN involvement			
		Absent	Present	*p*	Statistical test
Size (mean)		2.27	3.025	0.17	Mann Whitney-U
	Tı	10	9	0.51	Fisher's exact
	>T1	7	11		Fisher' s exact
Multifocality	Present	5	2	0.21	Fisher's exact
	Absent	12	18		
Nuclear grade	1-2	12	17	0.42	Fisher's exact
	3	5	3		
LVI	Present	7	12	0.33	Fisher's exact
	Absent	10	8		
Estrogen receptor	Present	13	18	0.38	Fisher's exact
	Absent	4	2		
SLN definition method	Frozen	15	19	0.58	Fisher's exact
	Other	2	1		
Involved SLN number (mean)		1.23	1.95	0.048	Mann Whitney-U
Un-involved SLN number (mean)		1.41	1.20	0.69	unpaired t

Table 1. Demographic characteristics of patients and histopathologic characteristics of tumors*

* This data is collected from both patients with and without non-SLN involvement among patients with SLN involvement.
(p<0.05, significant)

Table 2. Data provided from the nomogram application to our patients*

Nomogram data non-SLN involvement		Non-SLN involvement			
		Absent	*Present*	*p*	*Statistical test*
Prediction rate	≤%70	16	12	0.0227	Fisher's exact
	>%70	1	8		
(p<0.05, significant)					

* The nomogram has been developed at Memorial Sloan-Kettring Cancer Center to predict non-sentinel lymph node involvement rate among patients with sentinel lymph node involvement by Zee et al.

Whitney U test). There was no significant relationship between other data and non-SLN involvement (Table 1). Besides, statistically significant non-SLN involvement was observed among patients with non-SLN involvement probability of more than 70% (Fisher's exact test, p=0.022) (Table 2).

Discussion

Condition of ALN is the most important marker in breast cancer, and plays a role in adjuvant chemotherapy decision. In a study conducted by Strahlenter et al., it indicated that 53.4% of patients who underwent AD, were unnecessarily over-treated as they had no ALN involvement (7). SLN biopsy is an accepted method to determine ALN involvement. Currently, AD in all patients with SLN involvement is a standard approach. While non-SLN involvement is observed in 54.05% of SLN involved patients in this study, SLN involvement is observed only in 45.94% of patients. Fifty percent of patients have undergone unnecessary AD and inherited its possible morbidities. While Jhy-Cheng et al. also reported similar results, Kapur et al. stated in their study that only 32.7% AD performed patients had non-SLN involvement (1, 8).

Van Zee et al. developed a nomogram, which is based on tumor size, tumor type and nuclear grade, lymphovascular invasion, multifocality, estrogen receptor positivity, method to determine SLN metastasis, numbers of positive and negative SLN, to predict patients with non-SLN metastasis among patients with SLN metastasis at MSKCC in 2003 (4). AD is not proposed to patients, in whom AD-induced morbidities are to be avoided, with the use of this nomogram by indicating axillary involvement risks to patients preoperatively. Smidt et al. reported in their population based study that the predictive power of the nomogram was weak (9). Lambert et al. also added a tissue imprint method to the nomogram, and they reported that validity of nomogram developed by MSKCC still continued (5). When studies in which this nomogram is discussed, Smidt and Ponzone reported that this nomogram was a valid method, whereas Klar stated that it was not. Additionally, Kocsis stated that it was a weak method, whereas Zgajnar

reported that it showed non-SLN metastasis rates higher than normal (9, 10, 11, 12, 13).

The nomogram developed by Van Zee et al. may be helpful in predicting non-SLN involvement among breast carcinoma patients with SLN involvement. However, there are difficulties in providing some data which are used in the nomogram in the preoperative period. Tumor size is determined in the pathology specimens of patients, and can only be defined after the lesion is excised and pathologically evaluated. This will prevent it from being performed at the same session with SLN biopsy. Tumor size determined by physical examination or radiological imagining method will be different from that of measured by pathological tumor size. Besides, signs such as tumor type and nuclear grade, lymphovascular invasion, estrogen receptor positivity, are registered by pathological evaluation. This will also not enable us to decide if there is non-SLN metastasis at the same session by using the nomogram. On the other hand, preoperative non-SLN involvement may be predicted by detecting multifocality, defined by physical examination, and by radiological investigation. Again, if the decision for real multifocality presence is anticipated for pathological investigation by local excision or mastectomy, it will prevent availability of the nomogram preoperatively. While the number of positive and negative SLN evaluated during an operation requires assessment of all lymph nodes that are excised, an experienced and rapid evaluating pathology team should be present. It should be retained that this facility is not present in every hospital, whereas its presence would be difficult and yield an additional cost.

In summary, it is possible to avoid AD in some patients by defining factors affecting non-SLN involvement among patients with SLN involvement, which will be provided by preoperative data of patients and tumors. Currently, there is still an ongoing debate about many scoring systems, which may predict non-SLN involvement. Nomograms, which have been developed especially by using data from patient demographic characteristics, preoperative physical examination, radiological imagining, and pathological evaluation, will enable more distinctive treatment plans.

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